REMARKS

Claims

Claims 1, 2, 4–7 and 9–11 are currently under examination with claims 8, and 12–22 withdrawn from consideration due to restriction/election. Claim 3 is cancelled without prejudice or disclaimer.

Claim Amendments

The claims have been amended to use language in accordance with conventional US practice and do not raise new matter.

Drawings

New drawings are enclosed herewith.

Rejection under 35 U.S.C. § 112, first paragraph

The rejection, not specifically discussed herein, is moot in view of the amendment. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

The rejection of claims 1-7, and 9-11 under 35 U.S.C. §103(a) as allegedly unpatentable over Thorpe (US 6,703,020) is respectfully traversed.

To establish a prima facie case of obviousness, the prior art reference(s) must teach or suggest all the claim limitations. See, MPEP §2143 - §2143.03.

Thorpe generically discloses antibodies against VEGF receptor 2 (VEGFR2; which is also termed KDR/Flk-1) and use thereof in tumor regression. See, the paragraph bridging cols. 2 and 3 of Thorpe et al. The Examiner at page 8 of the Office Action alleges that it would have been prima facie obvious to one of ordinary skill in the art to combine moieties of the VEGF/VEGFR system and Angiopoietin/Tie2 receptor system as disclosed by Thorpe because "both receptor systems when acting in combination, retain the ability to inhibit the vascularization of endothelial cells." Applicants respectfully disagree with this contention. The cited reference does not recite a pharmaceutical composition comprising of at least one compound I and at least one compound II having the recited functional

properties. Thorpe only discloses the potential antitumor effects of a VEGFR inhibitor or a Tie2 inhibitor (i.e., as single agents). See, last paragraph at page 5 of the Office Action. As such, it is respectfully submitted that the subject matter of claims 1, 2, 4, 5 and 7 cannot be rendered obvious by the disclosure contained in Thorpe.

Regarding instant claims 10 and 11, it is respectfully submitted that insofar as the cited reference is silent with respect to the combination recited in Applicants' independent claim 1, the subject matter in these claims is also free of prior art.

It is further submitted that Thorpe does not render the claims obvious because the details and examples of the reference would point particularly to other types of mixtures. For example, in section C4 at col. 80 of the cited reference, Thorpe discloses angiopoietin-1 (Ang-1), and a naturally occurring receptor antagonist, angiopoietin-2 (Ang-2) as viable anti-angiogenic agents. It is further taught that angiopoietin-1 is generally required for the later stages of vascularization and promotes maintenance and stabilization of mature vessels. Thorpe discloses that angiopoietin-1 is thus a maturation or stabilization factor, thought to convert immature vessels to mature vessels by promoting interactions between endothelial cells and surrounding support cells, while angiopoietin-2 antagonizes this effect. As a rationale for employing angiopoietin-1 with a VEGFR antibody for anti-angiogenic effects, Thorpe expressly teaches that angiopoietin-1 does not have any significant downside and can be administered to prevent vascular remodeling or for its anti-inflammatory effects. However, Thorpe subsequently teaches away from this disclosure. In particular in the paragraph bridging cols. 80 and 81, Thorpe expressly recites that administration of angiopoietin-1 would inhibit the combined effects of angiopoietin-2 and VEGF, thus teaching away from the claimed subject matter:

> It is reasoned that using a tumor-binding ligand to deliver angiopoietin-1 to tumor blood vessels would readily deliver on the order of 500,000 angiopoietin-1 molecules to a vessel lumen. This would overwhelm the Tie2 receptor system, totally saturating the Tie2 receptors with the angiopoietin-1 ligand. Angiopoietin-2 would thus be unable to bind, and so the combined effects of angiopoietin-2 and VEGF (see discussion below) would be inhibited. (Emphasis added)

Moreover, in the paragraphs spanning cols. 28 and 36, Thorpe provides a laundry list of other "therapeutic agents" which may be combined with Thorpe's anti-VEGFR antibody. Such agents may include, radiotherapeutic agents (more than twenty

radioisotopes are disclosed in col. 129, lines 1–9), anti-angiogenic agents (more than three broad classes of such agents are recited in col. 80, section C4, and more than twenty specific subtypes are recited in section G2, col. 117), apoptosis-inducing agents (more than six different apoptosis-inducing genes recited in section G3 of col. 122), coagulation factors (more than a dozen factors recited in section C2, col. 76), and/or chemotherapeutic agents (more than two dozen "exemplary agents" are recited in section G1, col. 114 of Thorpe). However, such a combination is not exemplified in any of the examples. Based on the teachings of Thorpe, there would be no way, absent hindsight, to arrive at the specific combination recited in Applicants' claims, even if Thorpe had not taught against it.

It is therefore courteously submitted that Thorpe fails to teach or suggest all the elements of Applicants' claims. The Office Action is merely alleging one could arrive at the invention from the prior art. But this is insufficient. It is required that the PTO establish that one of ordinary skill would arrive at the claimed invention from the references. Therefore, it is respectfully submitted that the Office Action has failed to meet the basic criteria for *prima facie* case of obviousness, and as such, the rejection under 35 U.S.C. §103(a) must be withdrawn.

Withdrawal of the rejection is respectfully requested.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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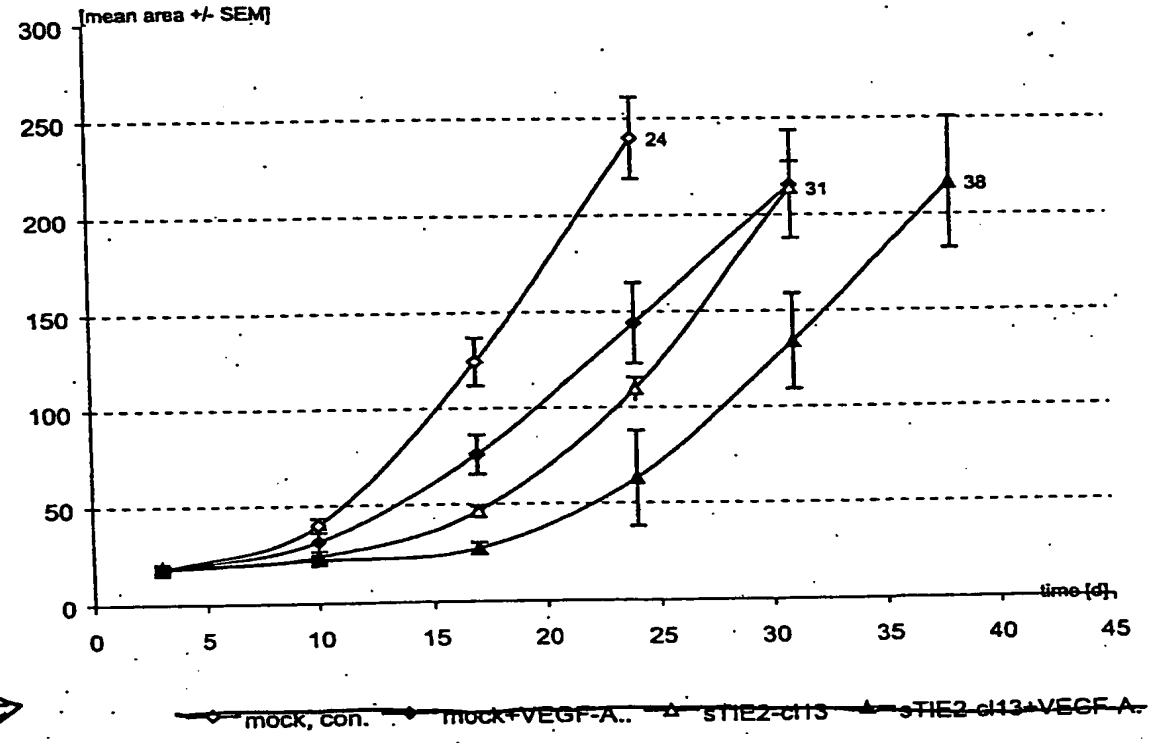

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Fig. 1

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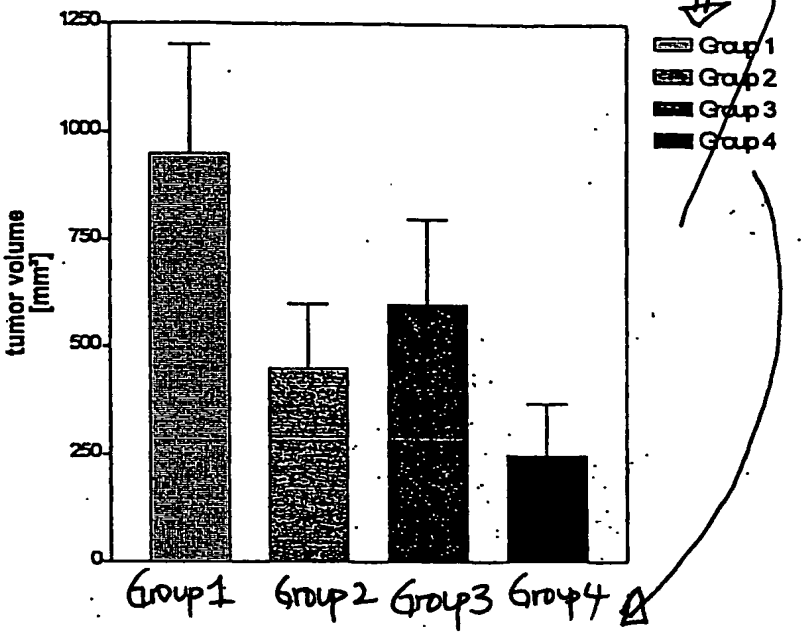

Fig. 2

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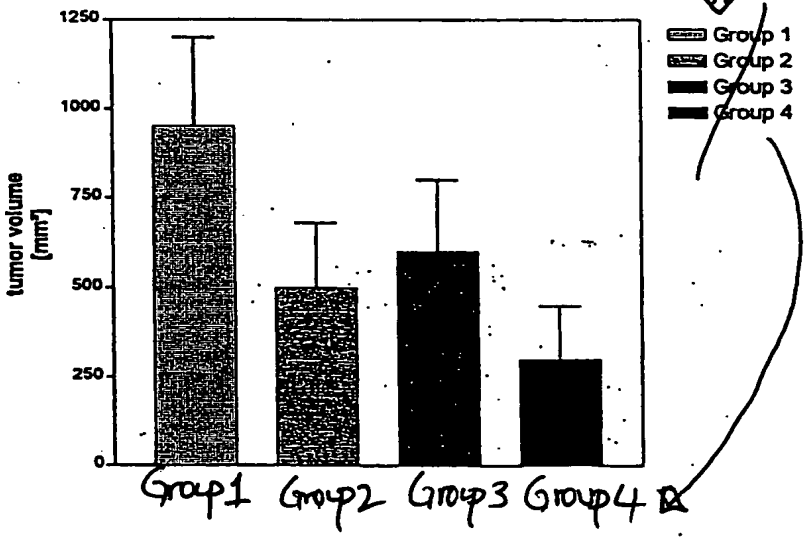

Fig. 3